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Research Article

Royal jelly maintains telomere length and antioxidant parameters in the pancreas of streptozotocin-induced rats

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Abstract

Background: Streptozotocin (STZ) is an agent with selective toxicity targeting pancreatic β-cells and is commonly used to establish models of pancreatic damage. Royal jelly (RJ) is a natural product rich in biologically active compounds and has been shown in various studies to exert antioxidative and cytoprotective effects.

Aims: This study aimed to evaluate the potential protective effects of RJ against STZ-induced pancreatic damage and to investigate these effects in terms of oxidative stress (OS) and telomere biology.

Methods: Twenty-four female Wistar albino rats were randomly divided into four groups: control, RJ (350 mg/kg), STZ, and STZ + RJ (350 mg/kg). Telomere length in pancreatic tissue and serum levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), paraoxonase-1 (PON1), and telomerase were analyzed using commercial enzyme-linked immunosorbent assay kits.

Results: STZ administration significantly increased oxidative DNA damage (8-OHdG) and decreased PON1 levels, indicating elevated OS. RJ treatment effectively reversed these changes, bringing 8-OHdG and PON1 levels closer to those of the control group. Moreover, RJ administration significantly increased the reduced pancreatic telomere length and serum telomerase levels in the STZ group.

Conclusion: These findings suggest that RJ may mitigate STZ-induced oxidative stress and telomere shortening. Further studies are needed to elucidate the therapeutic mechanisms of RJ in OS-related pancreatic disorders.

Özet

Dayanak: Streptozotosin (STZ), özellikle pankreasın β-hücrelerini hedef alan seçici toksisiteye sahip bir ajandır ve pankreatik hasar modellerinin oluşturulmasında sıklıkla kullanılmaktadır. Arı sütü (RJ) ise biyolojik olarak aktif bileşiklerce zengin doğal bir ürün olup oksidatif stres (OS) karşıtı ve hücre koruyucu etkileri çeşitli çalışmalarda gösterilmiştir.

Amaçlar: Bu çalışma, RJ'nin STZ ile indüklenen pankreas hasarına karşı potansiyel koruyucu etkilerini değerlendirmeyi ve bu etkileri oksidatif stres ile telomer biyolojisi açısından incelemeyi amaçlamıştır.

Yöntemler: Yirmi dört dişi Wistar albino sıçan rastgele dört gruba ayrılmıştır: Kontrol, RJ (350 mg/kg), STZ ve STZ + RJ (350 mg/kg). Pankreas doku örneklerinden telomer uzunluğu; kan serumundan da 8-hidroksi-2'-deoksiguanozin (8- OHdG), paraoksonaz-1 (PON1) ve telomeraz düzeyleri enzim bağlantılı immünosorbent analizi kitleri kullanılarak analiz edilmiştir.

Bulgular: STZ uygulaması, oksidatif DNA hasarını (8-OHdG) anlamlı derecede artırmış ve PON1 düzeylerini azaltarak artmış OS'yi ortaya koymuştur. RJ tedavisi bu değişiklikleri etkili bir şekilde tersine çevirerek 8-OHdG ve PON1 düzeylerini kontrol grubu değerlerine yaklaştırmıştır. Ayrıca, RJ uygulamasının STZ grubunda azalan pankreas telomer uzunluğunu ve serum telomeraz düzeyini anlamlı biçimde artırdığı belirlenmiştir.

Sonuç: Bu bulgular, RJ'nin STZ kaynaklı oksidatif stresi ve telomer kısalmasını azaltabileceğini göstermektedir. OS ile ilişkili pankreatik bozukluklarda RJ'nin terapötik mekanizmasını en iyi şekilde ortaya koymak için ileri çalışmalara ihtiyaç vardır.

Keywords: 8-OHdG, pancreas, PON1, royal jelly, streptozotocin, telomere length, telomerase

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Introduction

Royal jelly (RJ) is a nutrient-rich compound secreted by the hypopharyngeal glands of worker honey bees. It is a complex mixture of lipids, glucose, proteins, vitamins, and minerals. The longevity and fertility of queen bees have been attributed to their exclusive feeding on RJ (Özkök et al., 2021). RJ is widely utilized commercially in the medical and cosmetic fields. Animal studies have demonstrated that RJ possesses multiple bioactivities, including antioxidant (Ghanbari et al., 2016), anti-inflammatory (Fujiwara et al., 1990), antihypertensive (Tokunaga et al., 2004), and immunomodulatory (Vucevic et al., 2007) effects. One of its most remarkable properties is its ability to stimulate cell proliferation and influence antidiabetes therapeutic processes (Ghanbari et al., 2015).

Streptozotocin (STZ), is a monofunctional nitrosourea derivative isolated from *Streptomyces achromogenes*, which exhibits broad-spectrum antibiotic activity and antineoplastic properties. STZ is widely employed in experimental models to induce selective pancreatic β-cell damage due to its potent DNA-alkylating properties, resulting in random DNA synthesis, strand breaks, adducts, alkali-labile sites, micronuclei formation, sister chromatid exchanges, chromosomal aberrations, and cell death. These impacts render STZ a powerful mutagen in bacterial and mammalian cells (Tural Çifçi & Tuzcu, 2025; Paviolo et al., 2015). The selective uptake of STZ by pancreatic β-cells is mediated via the GLUT2 glucose transporter, leading to DNA alkylation and the subsequent activation of poly(ADP-ribose) polymerase, NAD^+ depletion, reduced ATP levels, and the inhibition of insulin production. Moreover, STZ generates reactive oxygen species, contributing further to DNA damage and cytotoxicity (Tural Çifçi & Tuzcu, 2025; Saha et al., 2025). STZ is administered to obtain experimental models, as either a single high dose or multiple low doses, to reliably induce diabetes, providing a reproducible platform for assessing pancreatic tissue responses to pharmacological agents independent of systemic glucose levels (Lenzen, 2008; Like & Rossini, 1976).

Telomeres are specialized nucleoprotein complexes located at the ends of linear chromosomes, playing a crucial role in preserving genomic stability and cell replicative capacity (Blackburn, 1991). Telomere shortening, which occurs naturally with each cell division, may be further accelerated by external factors such as oxidative stress (OS) and DNA damage, leading to cell senescence or apoptosis (Epel et al., 2004). In this context, telomere length is not only a biomarker of cell aging but also a critical determinant of cell proliferative potential (Blackburn, 2001). Since pancreatic β-cell regeneration is limited and sensitive to OS, monitoring telomere integrity provides valuable insights into tissue homeostasis under pathological conditions (Zhang et al., 2019). Furthermore, OS-induced telomere attrition has been implicated in the dysfunction of several tissues, including pancreatic islets, making telomere dynamics a relevant parameter for metabolic and degenerative diseases (Epel et al., 2004; Zhang et al., 2019).

This study primarily aimed to evaluate the potential of RJ, a natural bioactive compound, to mitigate STZ-induced β-cell damage. Specifically, considering the antioxidant, antiapoptotic, and cytoprotective properties of RJ, this study investigated its impacts on STZ-induced DNA damage, OS, and telomere dysfunction. Overall, it elucidates the alleviative potential of RJ against STZ-induced pancreatic injury and the contribution of natural bioactive agents in maintaining pancreatic homeostasis under metabolic and genotoxic stress.

Materials and Methods

This study was carried out with the approval of Çanakkale Onsekiz Mart University Animal Experiments Local Ethics Committee (approval number: 2021/01-01, dated: 12.02.2021).

Experimental Plan

The RJ used is commercially available and is produced by the BeeO R&D Laboratory, İstanbul Technical University, İstanbul, Türkiye. The RJ dose administered was determined based on the effective doses reported for similar animal models (Çakır, 2023). For the experiments, 24 Wistar albino female rats weighing 200–250 g were divided into four groups, with six rats in each group. They were named as control, RJ (350 mg/kg RJ), STZ, and STZ + RJ (350 mg/kg RJ) groups (Figure 1). The environmental conditions were maintained at 21 °C ± 2 °C and 50% ± 5% humidity, under a 12/12 h light/dark cycle. The STZ group animals were intraperitoneally (i.p.) administered with 50 mg/kg STZ in citrate buffer. RJ was administered by the gavage method. At the end of the 4-week experiment, the rats were kept on a fast for 10 h and anesthetized with 70 mg/kg ketamine and 7 mg/kg xylazine (i.p.). Blood was collected from their hearts after puncture and transferred to tubes without an anticoagulant for serum. After the tubes were spun in an NF 1200 centrifuge (Nüve, TX, USA) at 1,400 g and 4 °C for 10 min, the serum was separated and stored in labeled tubes at -80 °C.

Serum Analysis

In the study, commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to measure telomerase level (E-EL-R0947; Elabscience, TX, USA), 8′-hydroxy-2′-deoxyguanosine (8-OHdG, MBS701076; MyBiosource, CA, USA) levels, and PON1 (MBS453155; MyBiosource) contents. An ELx800 ELISA device (BioTek Instruments, Inc., VT, USA) and an ELx50 washer (BioTek) were used.

Tissue Homogenization

A clinic/cell SV mini tissue extraction kit (108-101; GeneAll Biotechnology Co., Ltd., Seoul, Korea), 0.2 mm stainless steel beads, and a Digital Disruptor Cell Disruptor (#3591456; Bio-Rad Laboratories, CA, USA) were employed to homogenize the pancreatic tissues.

Telomere Lengths

In this study, the average telomere length of the pancreatic tissue cells was determined using the Telomere Length Quantification qPCR Test Kit (R8918; ScienCell Research Laboratories, CA, USA) and the Absolute Rat Telomere Length Kit (R8918;

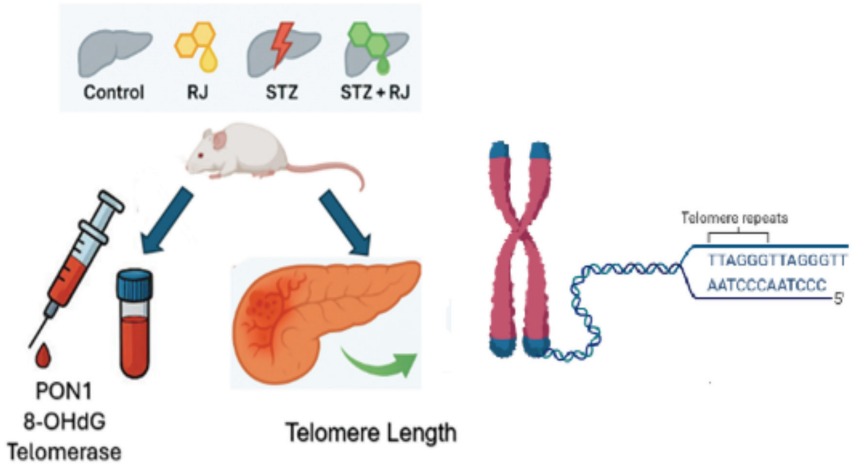

Figure 1. Experimental plan.

ScienCell Research Laboratories). A single-copy reference (SCR) primer, which amplifies a 100-bp region of chromosome 17, was employed for data normalization. Genomic DNA with a known telomere length served as a reference for calculating the telomere lengths of the study samples.

ΔCq (TEL) = Cq (TEL, target sample)- Cq (TEL, reference sample)

ΔCq (SCR) = Cq (SCR, target sample)- Cq (SCR, reference sample)

$\Delta\Delta Cq = \Delta Cq$ (TEL)- ΔCq (SCR) = Telomere length of reference sample $\times 2^{-\Delta\Delta Cq}$

The average telomere length in the target genomic DNA was 5.05 ± 0.18 Mb. Rat diploid cells have 84 telomeres; the average length of each telomere is = 5.05 ± 0.18 Mb/84 = 60.1 ± 2.1 kb per diploid cell or chromosome end (Çakır, 2023; O'Callaghan & Fenech, 2011).

Statistical Analysis

All data are expressed as mean ± standard deviation (SD). Normality and homogeneity of variances were assessed using the Shapiro–Wilk and Levene tests, respectively. Variables with homogenous variances were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's post-hoc test, while variables with unequal variances were analyzed using Welch ANOVA, followed by Games–Howell post-hoc comparisons. Statistical significance was set at $p < 0.05$, and post-hoc differences are indicated in the tables as $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$. All analyses were performed using GraphPad Prism 9 (GraphPad Software, CA, USA).

Results

The serum 8-OHdG levels varied markedly among the groups (Table 1). They declined and elevated significantly in the RJ and STZ groups, respectively, compared to the control ($p < 0.001$). Co-treatment with RJ and STZ significantly reduced 8-OHdG levels compared to STZ alone ($p < 0.001$), although the contents of both groups remained slightly higher than that of the control group ($p < 0.05$).

Table 1. Serum 8-OHdG levels (ng/mL).

Group	Mean ± SD	Post-hoc
Control	1.445 ± 0.011	*
RJ	1.253 ± 0.034	**
STZ	1.718 ± 0.021	***
STZ + RJ	1.465 ± 0.046	*

8-OHdG: Group means ± SD. Normality was confirmed ($p > 0.05$), but homogeneity of variances was not confirmed according to Levene's test. Therefore, group differences were analyzed using Welch ANOVA, followed by Games–Howell post-hoc test for pairwise comparisons, and significance levels are indicated in the table as $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$.

PON1 activity differed remarkably between the groups (Table 2). It significantly increased and decreased in the RJ and STZ groups, respectively, compared to the control group ($p < 0.001$). STZ and RJ cotreatment increased PON1 activity compared to STZ alone, restoring it closer to the control group levels ($p < 0.05$).

The pancreatic tissue telomere lengths varied significantly among the groups (Table 3). The telomere length decreased markedly in the STZ group but increased significantly in the STZ + RJ group compared to the STZ group ($p < 0.01$), although it was not fully restored to the same length as the control group.

The serum telomerase levels also differed among the groups (Table 4). They declined markedly in the STZ group, but did not differ significantly in the RJ and STZ + RJ groups, compared to the control group ($p > 0.05$). these findings indicate that RJ administration partially mitigated such STZ-induced decrease.

Table 2. Serum PON1 activity (U/mL).

Group	Mean ± SD	Post-hoc
Control	218.7 ± 4.4	*
RJ	229.7 ± 7.4	**
STZ	187.0 ± 2.6	***
STZ + RJ	212.0 ± 5.0	*

PON1: Values are presented as mean ± SD. Normality and homogeneity of variances were confirmed, and group differences were analyzed using one-way ANOVA, followed by Tukey's post-hoc test. Significance levels are indicated as *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

Table 3. Pancreatic telomerase length (kb).

Group	Mean ± SD	Post-hoc
RJ	96.64 ± 3.10	*
Control	100.94 ± 1.84	*
STZ	7.31 ± 0.29	***
STZ + RJ	44.82 ± 0.32	**

Telomere length: Values are presented as mean ± SD. Normality and homogeneity of variances were confirmed, and group differences were analyzed using one-way ANOVA, followed by Tukey's post-hoc test. Significance levels are indicated as *$p < 0.05$, **$p<0.01$, and ***$p < 0.001$.

Table 4. Serum telomerase levels (ng/mL).

Group	Mean ± SD	Post-hoc
Control	0.398 ± 0.036	*
RJ	0.348 ± 0.037	*
STZ	0.281 ± 0.064	**
STZ + RJ	0.348 ± 0.046	*

Telomerase levels: Values are presented as mean ± SD. Normality and homogeneity of variances were confirmed, and group differences were analyzed using one-way ANOVA, followed by Tukey's post-hoc test. Significance levels are indicated as *$p < 0.05$, **$p < 0.01$.

Discussion

STZ is widely employed to construct experimental diabetes models due to its selective cytotoxicity toward pancreatic β-cells within the islets of Langerhans. Structurally similar to glucose, STZ enters β-cells via the GLUT2 transporter and induces cell damage through mechanisms including DNA alkylation, nitric oxide production, and free radical generation. This process not only suppresses insulin biosynthesis but also promotes profound OS and inflammation in pancreatic tissues (Fu et al., 2010; Lenzen, 2008). In the present study, a single intraperitoneal dose of 50 mg/kg STZ was administered to initiate tissue-level pancreatic injury. This dosage has been identified as optimal, since lower doses (30–40 mg/kg) failed to elicit a consistent diabetic response, and higher doses (≥70 mg/kg) were associated with severe systemic toxicity and increased mortality (Ar'Rajab & Ahrén, 1993).

Beyond its use in diabetes modeling, STZ induces persistent genomic instability. Studies in rat-derived ADIPO-P2 cells demonstrated that STZ exposure triggers long-term telomeric dysfunction, characterized by a loss in telomere FISH signals and duplications, independent of telomerase level or telomere length (Paviolo et al., 2015). Similarly, *in vivo* studies reveal that STZ damages the DNA of the proximal tubular epithelial cells and activates p53-based signaling pathways, leading to site-specific cytotoxicity, which, in certain contexts, could be mitigated pharmacologically (Nakai et al., 2023). In neuronal models, differentiated SH-SY5Y cells displayed altered sensitivity to STZ-induced cytotoxicity and insulin resistance, highlighting the role of cell maturity in the STZ response (Bagaméry et al., 2021). Additionally, STZ induces retinal progenitor cell damage in neonatal rats independent of hyperglycemia, suggesting direct cytotoxic effects in developing tissues (Lin et al., 2024).

The health-benefiting influence of RJ stems from its rich composition of bioactives. RJ contains flavonoids and phenolics known for their potent antioxidant activity, enabling it to counteract OS implicated in the pathogenesis of various diseases (Kocot et al., 2018). Furthermore, major RJ proteins (MRJPs) and peptides derived from RJ demonstrate metal-chelating as well as antioxidant capabilities involving mechanisms such as hydrogen peroxide, superoxide, and hydroxyl radical scavenging. The proteolysis of RJ proteins produces peptides that exhibit a robust antioxidant potential (Guo et al., 2021).

Given the increasing interest in natural bioactive compounds, this study aimed to evaluate the potential protective effects of RJ against STZ-induced pancreatic injury, with particular attention to telomere length as a molecular indicator of cell viability. In addition, oxidative state alterations were assessed using specific biomarkers, 8-OHdG for DNA oxidative damage and PON1 for enzymatic antioxidant status, to elucidate the redox-modulatory role of RJ within the pancreatic microenvironment (Aviram & Rosenblat, 2004; Kasai, 1997; Mackness et al., 2004; Valavanidis et al., 2009).

In addition to telomere length, serum telomerase level was also evaluated to gain insights into the status of telomere maintenance mechanisms following STZ-induced pancreatic damage and to assess the modulatory effects of RJ on this process. Although serum telomerase levels may not fully reflect tissue-level enzyme activity, they can provide complementary information regarding systemic telomere dynamics (Kim & Wu, 1997).

The toxic effects of STZ are not limited to the selective damage of pancreatic β-cells but also to an increased systemic OS burden (Lenzen, 2008; Szkudelski, 2001). However, RJ administration increased PON1 activity and significantly reduced 8-OHdG concentrations. These results suggest that RJ exerts protective effects not only by alleviating oxidative DNA damage but also by reducing lipid peroxidation.

These results of previous studies support these findings. For instance, Çakır (2023) demonstrated that RJ markedly enhanced

PON1 activity and suppressed 8-OHdG concentrations during liver toxicity induced in rats. Similarly, Çakır (2022) reported that different doses of RJ exerted beneficial effects on OS, as indicated by biomarker levels and telomerase level in rats exposed to cadmium. Prior investigations have emphasized the effectiveness of RJ in alleviating diabetes-associated biochemical disturbances and OS from various perspectives. Moreover, RJ promotes healing by stimulating cell division and tissue regeneration (El-Seedi et al., 2024; Oršolić & Jazvinšćak Jembrek, 2024). PON1 exerts beneficial effects in various diseases, including diabetes, by modulating the signaling pathways associated with inflammation and OS (Marsillach et al., 2009). The decrease in PON1 activity following cisplatin administration was extensively preserved in rats treated with RJ (Yildirim et al., 2012). Similarly, in the present study, STZ administration suppressed the PON1 activity, which were restored to near-control values following RJ treatment.

8-OHdG is a well-established biomarker used to detect base modifications induced by mutagenic damage to DNA and RNA (Alper et al., 2005; Wong et al., 2006). Experimental diabetes models have also demonstrated elevated OS marker and 8-OHdG levels, highlighting the oxidative nature of diabetic damage and the role of 8-OHdG as a molecular indicator of this process (Alper et al., 2005; Mis et al., 2018). In this study, plasma 8-OHdG concentrations were consistently and remarkably enhanced in STZ-treated rats compared to controls. The notable reduction in 8-OHdG levels following RJ administration is attributed to the potent antioxidant properties of RJ.

The findings of the present study are consistent with those reported in the literature, indicating that telomere integrity and telomerase level are closely associated with tissue damage, OS, and inflammation. Processes such as genome instability, heterochromatin loss, and telomere attrition accelerate cell senescence and aging, particularly under conditions of tissue injury and inflammatory stress (Wu et al., 2024). Comprehensive meta-analyses investigating the relationship between telomere dynamics and OS have provided substantial evidence that, although complex, OS accelerates *in vivo* telomere attrition, especially in studies employing structural telomere measurements such as TRF (Armstrong & Boonekamp, 2023). Similarly, Tilekli et al. (2024) reported that OS and proinflammatory responses directly affect telomere length, and that diets low in saturated fats or high in unsaturated fats, along with regular physical activity, help maintain telomere integrity.

Conversely, several studies have demonstrated that telomerase can be activated to a limited but critical level during regenerative processes. Notably, TERT expression-based interventions using adeno-associated viral vectors improved tissue function, reduced the levels of molecular aging markers, and remarkably extended lifespan even in adult and aged models (Bernardes de Jesus et al., 2012). These findings suggest that telomerase level may play a decisive role in tissue regeneration and post-injury recovery processes.

In this study, telomerase levels reached statistical significance following RJ administration. Telomere attrition accelerates under conditions of increased metabolic activity and inflammatory burden, and this effect may vary between species, methods, and tissues (Simoroz et al., 2025). Therefore, the marked reduction in telomerase levels observed in the STZ group and the increase seen in the RJ group reflect a pattern consistent with the literature.

The telomere length in the RJ group increased significantly, but did not fully reach the control levels, which can be attributed to persistent telomeric damage induced by STZ. As a potent DNA-methylating agent, STZ causes persistent structural alterations at the telomeric regions, which manifest as telomere dysfunction, instability, and associated chromosomal aberrations at the cytogenetic level (Paviolo et al., 2015). Under such persistent damage, even if regenerative mechanisms are activated, complete restoration of telomere integrity may not be achievable. Thus, the substantial improvement in telomere structure induced by RJ, yet not achieving control levels, can be considered a consequence of STZ-induced long-lasting telomeric injury.

Although telomeres naturally shorten with each cell division, certain factors, particularly tissue injury, can accelerate this process (Çakır, 2023; Epel et al., 2004). Telomerase activity can be readily monitored in continuously dividing cells such as cancer cells; however, its detection in somatic tissues is considerably more challenging (Blackburn, 1991). Telomerase activity can be observed during tissue regeneration processes (Cherif et al., 2003; Çakır, 2022, 2023; Shay & Bacchetti, 1997). In a study monitoring the regenerative status of rat pancreatic tissues, telomerase was found to be actively regulated (Oh et al., 2002).

A study investigating the applicability of telomere length as a biomarker of cell aging and tissue damage reported a remarkable shortening of the telomere in type 2 diabetes (Tarry-Adkins et al., 2021). Jiang et al. (2018) demonstrated that MRJPs exert anti-aging effects in human fibroblast cell lines and also enhance the number of cells with longer telomeres under *in vivo* conditions. Additionally, MRJPs elevate DNA and protein synthesis by modulating four age-related genes: *MTOR*, *SOD1*, *CTNNB1*, and *TP53* (Jiang et al., 2018). A cell viability assay highlighted the stimulatory effects of RJ on stem cell growth (Özkök et al., 2021). Similarly, Çakır (2023) reported that RJ improved telomere length, antioxidant parameters, and serum biochemical markers in rats with CCl_4-induced liver injury. RJ promotes cell survival, proliferation, and antioxidant responses while protecting telomeres during cell crises (Jenkhetkan et al., 2017). Furthermore, RJ protects human cells from genotoxicity, potentially through its antiapoptotic, antioxidative, and antiaging properties (Jenkhetkan et al., 2018). In this study, STZ administration markedly reduced telomere length in pancreatic cells, whereas RJ supplementation at the dose applied remarkably improved telomere integrity.

Conclusion

The findings of the present study indicate that RJ protects against STZ-induced pancreatic damage primarily by attenuating OS and supporting telomere integrity. STZ significantly increased oxidative DNA damage (8-OHdG levels) and reduced PON1 activity, confirming elevated OS levels. RJ effectively reversed these changes, restoring 8-OHdG and PON1 levels similar to those of the control group. Additionally, RJ partially improved telomerase level and telomere length, but not to levels occurring in the control group. This partial reversal of STZ-induced telomere shortening can be attributed to persistent DNA methylation and telomere dysfunction caused by STZ, which have been shown to result in lasting telomere instability. Further detailed investigations are warranted to better elucidate the bioactive components and therapeutic potential of RJ.

Ethics

Ethics Committee Approval: This study was carried out with the approval of Çanakkale Onsekiz Mart University Animal Experiments Local Ethics Committee (approval number: 2021/01-01, dated: 12.02.2021).

Data Sharing Statement: All data are available within the study.

Footnotes

Conflict of Interest: The author(s) have no conflicts of interest to declare.

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